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Association between prehypertension and chronic kidney disease in the Japanese general population

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The increased prevalence of chronic kidney disease (CKD) is a consequence of the accumulation of risk factors, one of which is hypertension. Here we assessed the prevalence of CKD according to blood pressure among 232,025 patients in a Japanese nationwide database with a focus on the prevalence and risk factors of CKD in prehypertension. Patients were stratified by blood pressure and included 75,474 with optimal blood pressure (less than 120/80 mm Hg); 59,194 with prehypertension and a normal blood pressure (120–129/80–84 mm Hg) or 46,547 patients with high-normal blood pressure (130–139/85–89 mm Hg); and 50,810 with hypertension (over 140/90 mm Hg without anti-hypertensive drugs). CKD was defined as an estimated glomerular filtration rate of stage 3 or lower or having proteinuria greater than 1+ by a dipstick method. The prevalence of CKD among patients with optimal blood pressure, prehypertension having normal or high-normal blood pressure, and hypertension was 13.9, 15.6, 18.1, and 20.7% in men, and 10.9, 11.6, 12.9, and 15.0% in women, with a significant difference between genders at each strata of blood pressure. In men, but not in women, whose blood pressure was high-normal, the CKD risk was significantly greater (odds ratio 1.11) than those with optimal blood pressure. Obesity (body mass index over 25) was significantly associated with an increased risk of CKD in both men and women (odds ratio 1.43 and 1.26, respectively), and there was an additive effect of obesity and pre-hypertension on CKD risk in men compared with men with optimal blood pressure. Thus, the prevalence of CKD increased with the severity of blood pressure. Prehypertension with high-normal blood pressure, particularly in conjunction with obesity, was found to be an independent risk factor of CKD in men.

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Chronic kidney disease (CKD) is now recognized as a major global public health problem.[1,2] It is increasingly apparent that CKD is associated with increased risk of not only progression to renal failure but also excess cardiovascular morbidity and mortality in a manner independent of other known risk factors.[1,2]

CKD affects 10–15% of the adult population worldwide.[3,4] A recent Japanese survey demonstrated that the prevalence of CKD increased significantly in men, but not in women, from the 1970s to the 2000s in the general population.[5] The reasons are not well understood, but it is likely that the increased prevalence of CKD is a consequence of the accumulation of risk factors, such as hypertension or metabolic abnormalities including diabetes, dyslipidemia, and obesity, over the last three decades.[5] Furthermore, Japan is known to have a high incidence of end-stage renal disease, and the number of patients undergoing dialysis has been increasing.[6,7] The incidence and prevalence of end-stage renal disease are higher in men than in women in Japan.[8,9] Individuals with CKD have reduced life expectancy, and the social burden of CKD with or without end-stage renal disease is becoming greater. Accordingly, it should be a public health priority to identify CKD-prone high-risk subjects in the general population and to treat risk factors in the initial phase of CKD in order to prevent and delay the progression to renal failure. Such efforts would also help to prevent cardiovascular diseases.

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Hypertension is well established as both a cause and consequence of CKD.[10–12] In Asian countries in particular, high blood pressure (BP) is the strongest risk factor for renal outcome.[10] A previous study in Japan demonstrated that there was a linear continuous association between BP and incidence of end-stage renal disease; even in subjects without hypertension (i.e., even in subjects with prehypertension: systolic BP/diastolic BP, 120–139/80–89 mm Hg), there was a greater risk of future development of end-stage renal disease compared with the risk in subjects with optimal BP (<120/80 mm Hg).[11] Given the evidence that the risk of end-stage renal disease is increased throughout the BP range, understanding the burden of CKD in subjects with prehypertension could help in promoting prevention and screening efforts for both CKD and prehypertension.[13] Recently, the National Health and Nutrition Examination Survey in the United States demonstrated that the prevalence of CKD among those with prehypertension was 17.3%, compared with 13.4% in those with optimal BP.[14] However, there has been no comparable analysis of a nationwide database in Japan.

Accordingly, in the present study, we examined the prevalence of CKD within BP classification using a large nationwide database of subjects recruited from the national health checkup system in Japan. In addition, we examined some clinical characteristics other than BP that are prone to increase risk of CKD.

RESULTS

Patient characteristics

By reviewing the data from the national health checkup program in Japan, we identified 346,942 subjects for whom all the clinical data required for the present analysis were available. A total of 84,854 subjects with a history of treatment with anti-hypertensive medications, 12,771 subjects with a previous history of cardiovascular diseases, and 17,049 subjects with both were excluded from the present analysis. Moreover, 243 subjects with CKD stage 5 (estimated glomerular filtration rate (eGFR) < 15 ml/min per 1.73 m^2) were excluded. Table 1 shows the clinical characteristics of all subjects included in the present study ($n = 232,025$, left column) or the clinical characteristics according to gender difference (right column).

BP classification

Among the study subjects, 75,474 subjects (32.5%) had optimal BP, 105,741 subjects (45.6%) had prehypertension (normal BP: 59,194 subjects, 25.5%; high-normal BP: 46,547 subjects, 20.1%), and 50,810 subjects (21.9%) had hypertension. As the prevalence of such BP classification differed between men and women, the clinical characteristics according to BP classification were described by gender (Table 2). In accordance with the severity of BP classification, significant increases of age and body mass index, and significant decrease in the prevalence of current smoking, were observed. Information about glucose and lipid parameters could be obtained in some subjects, although not all: according to the severity of BP classification, there were significant differences in the glucose and lipid parameters (Supplementary Table S1 online).

CKD and BP classification

A total of 32,692 subjects (14.1%) were diagnosed with CKD, and 8751 subjects (3.8%) had proteinuria (≥1+). There was a gender difference in the prevalence of CKD (17.0% in men versus 12.2% in women; $P < 0.001$); accordingly, we determined the relationship between prevalence of CKD and BP classification separately for each gender (Table 2).

Table 1 | Characteristics of the study population overall (left column) or by gender (right column)

		Gender difference		
	Total subjects (*n*=232,025)	Women (*n*=142,293)	Men (*n*=89,732)	*P*-value
Age, years	**61.8 ± 9.4**	62.0 ± 9.1	61.4 ± 9.9	<0.001
Men, *n* (%)	**89,732 (38.7)**	—	89,732 (100)	<0.001
Body mass index, kg/m^2	**22.6 ± 3.2**	22.2 ± 3.2	23.4 ± 3.0	<0.001
Obesity, *n* (%)	**58,061 (25.0)**	29,358 (20.6)	28,703 (32.0)	<0.001
Current smoker, *n* (%)	**36,058 (15.5)**	9912 (7.0)	26,146 (29.1)	<0.001
Daily drinker, *n* (%)	**50,495 (21.8)**	12,471 (8.8)	38,024 (42.4)	<0.001
eGFR, ml/min per 1.73m^2	**76.9 ± 16.0**	76.9 ± 15.9	76.8 ± 16.3	0.57
CKD, *n* (%)	**32,692 (14.1)**	17,409 (12.2)	15,283 (17.0)	<0.001
Stage 1 and 2, *n* (%)	**7041 (3.0)**	3232 (2.3)	3809 (4.2)	<0.001
Stage 3, *n* (%)	**25,547 (11.0)**	14,117 (9.9)	11,430 (12.7)	
Stage 4, *n* (%)	**104 (0.04)**	60 (0.04)	44 (0.05)	
Proteinuria (≥1+), n (%)	**8751 (3.8)**	3948 (2.8)	4803 (5.4)	<0.001
BP measurement				
Systolic BP, mm Hg	**126 ± 17**	124 ± 17	128 ± 17	<0.001
Diastolic BP, mm Hg	**75 ± 11**	73 ± 10	77 ± 11	<0.001

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
Data are expressed as the means ± SD or percentage. *P*-values were obtained by an unpaired *t*-test or χ^2-test between women and men. Statistical significance was defined as $P < 0.05$. Obesity was defined as body mass index (BMI) ≥ 25 kg/m^2, and CKD was defined as eGFR < 60 ml/min per 1.73 m^2 and/or presence of proteinuria (≥1+). The proteinuria number in each column includes all stage 1/2 patients plus a few in stage 3/4.

Table 2 | Patient characteristics and BP values according to the BP classification by gender

	Women (*n*=142,293)					Men (*n*=89,732)				
	Optimal BP (*n*=51,715)	Prehypertension with normal BP (*n*=36,182)	Prehypertension with high-normal BP (*n*=27,348)	Hypertension (*n*=27,048)	*P*-value	Optimal BP (*n*=23,759)	Prehypertension with normal BP (*n*=23,012)	Prehypertension with high-normal BP (*n*=19,199)	Hypertension (*n*=23,762)	*P*-value
Age, years	58.8 ± 10.2	62.7 ± 8.4	64.4 ± 7.5	64.8 ± 7.2	<0.001	59.0 ± 10.7	61.0 ± 10.1	62.9 ± 9.3	63.0 ± 8.8	<0.001
Body mass index, kg/m^2	21.4 ± 2.9	22.2 ± 3.1	22.7 ± 3.2	23.2 ± 3.5	<0.001	22.5 ± 2.8	23.3 ± 2.9	23.6 ± 3.0	24.0 ± 3.1	<0.001
Obesity, *n* (%)	6775 (13.1)	7349 (20.3)	6863 (25.1)	8371 (30.9)	<0.001	5256 (22.1)	7168 (31.1)	6689 (34.8)	9590 (40.4)	<0.001
Current smoker, *n* (%)	4852 (9.4)	2234 (6.2)	1488 (5.4)	1338 (4.9)	<0.001	7953 (33.5)	6562 (28.5)	5071 (26.4)	6560 (27.6)	<0.001
Daily drinker, *n* (%)	4594 (8.9)	3120 (8.6)	2350 (8.6)	2407 (8.9)	0.33	8059 (33.9)	9428 (41.0)	8713 (45.4)	11,824 (49.8)	<0.001
eGFR, ml/min per 1.73m^2	77.8 ± 15.9	76.9 ± 15.9	76.1 ± 15.7	75.8 ± 15.8	<0.001	78.1 ± 16.5	77.0 ± 16.1	76.1 ± 16.0	76.0 ± 16.4	<0.001
CKD, *n* (%)	5619 (10.9)	4204 (11.6)	3540 (12.9)	4046 (15.0)	<0.001	3303 (13.9)	3582 (15.6)	3475 (18.1)	4923 (20.7)	<0.001
Stage 1 and 2, *n* (%)	864 (1.7)	672 (1.9)	650 (2.4)	1046 (3.9)	<0.001	729 (3.1)	799 (3.5)	814 (4.2)	1467 (6.2)	<0.001
Stage 3, *n* (%)	4774 (9.2)	3516 (9.7)	2874 (10.5)	2983 (11.0)	<0.001	2565 (10.8)	2775 (12.1)	2652 (13.8)	3438 (14.5)	<0.001
Stage 4, *n* (%)	11 (0.02)	16 (0.04)	16 (0.05)	17 (0.06)	<0.001	9 (0.03)	8 (0.03)	9 (0.04)	18 (0.07)	<0.001
Proteinuria (⩾1+), *n* (%)	1040 (2.0)	812 (2.2)	796 (2.9)	1300 (4.8)	<0.001	872 (3.7)	1003 (4.4)	1013 (5.3)	1915 (8.1)	<0.001
BP measurement										
Systolic BP, mm Hg	107 ± 8	123 ± 4	133 ± 4	149 ± 12	<0.001	109 ± 7	123 ± 4	132 ± 4	148 ± 13	<0.001
Diastolic BP, mm Hg	65 ± 7	73 ± 7	77 ± 7	85 ± 10	<0.001	67 ± 7	75 ± 6	79 ± 7	88 ± 10	<0.001

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
Data are expressed as the means ± SD or percentage. Obesity was defined as body mass index (BMI) ⩾25 kg/m^2, and CKD was defined as eGFR <60 ml/min per 1.73 m^2 and/or presence of proteinuria (⩾1+). The proteinuria number in each column includes all stage 1/2 patients plus a few in stage 3/4.

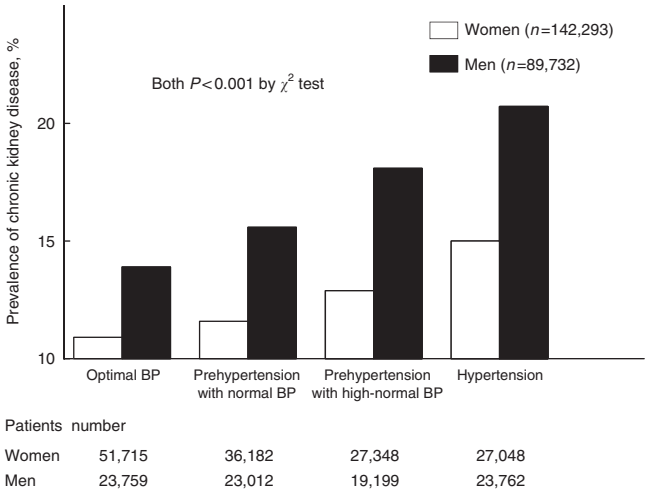

Figure 1 | Prevalence of chronic kidney disease according to the blood pressure (BP) classification in women (white bar) and men (black bar). The gender difference in the prevalence of chronic kidney disease increased in accordance with the severity of BP classification. Chronic kidney disease was defined as estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2 and/or the presence of proteinuria (⩾1+).

The prevalence of CKD and/or proteinuria (⩾1+) paralleled the severity of BP classification in both genders (Figure 1). The gender difference of CKD became greater and more prominent with increasing severity of BP classification.

Using multiple logistic regression analysis, the odds ratio for the presence of CKD was estimated. Hypertension was significantly associated with CKD in both genders. In contrast, only in men, but not in women, prehypertension with high-normal BP was significantly associated with an increased risk of CKD even after adjustment for confounders, such as age, obesity, current smoking, and daily drinking (Table 3). We also reanalyzed the results of Table 3 after adjusting for serum glucose, triglyceride, high-density lipoprotein, and low-density lipoprotein levels: these factors had no influence on the association between prehypertension with high-normal BP and CKD in men (data not shown).

Lifestyle factors, obesity, and CKD

Obesity was positively associated with CKD in both genders, and eGFR was significantly decreased in the subjects with obesity compared with those without obesity (76.1 ± 16.2 versus 77.1 ± 16.0 ml/min per 1.73 m^2; $P<0.001$). When we reanalyzed the risk of CKD conferred by obesity in either the subjects with low eGFR (<60 ml/min per 1.73 m^2) or the subjects with proteinuria (⩾1+), the conclusion remained unchanged (data not shown). In contrast, daily drinking was inversely associated with CKD in both genders. Additional analysis of the subgroup of subjects for whom daily alcohol intake data were available ($n=70,416$ men and $n=75,416$ women) revealed that the inverse association between daily drinking and CKD was consistent regardless of the amount of daily intake (⩾23 g of ethanol or <23 g of ethanol) in men (odds ratio (95% confidence interval, CI): 0.77 (0.73–0.80) and 0.89 (0.84–0.95), respectively; both $P<0.001$); in women, the inverse association between daily drinking and CKD was found only in those with a daily intake of <23 g of ethanol (odds ratio (95% CI): 0.91 (0.84–0.99); $P=0.03$).

In women, current smoking status was positively associated with CKD. In contrast, among men, current smoking was inversely associated with CKD; that is, male current smokers had a significantly higher level of eGFR than current non-smokers (mean (95% CI) of eGFR: 79.0 (78.8–79.2) versus 75.9 (75.8–76.1) ml/min per 1.73 m^2; $P<0.001$). In contrast, there was no significant difference in eGFR between female current smokers and non-smokers (mean (95% CI) of eGFR: 77.0 (76.7–77.3) versus 76.9 (76.8–77.0) ml/min per 1.73 m^2; $P=0.45$). When we reanalyzed the association of current smoking with the presence

Table 3 | Odds ratio (95% confidence interval) for CKD by gender

	Women (*n*=142,293)		Men (*n*=89,732)	
	Odds ratio (95% confidence interval)	*P*-value	Odds ratio (95% confidence interval)	*P*-value
Age, 10 years	1.39 (1.37:1.42)	<0.001	1.82 (1.78:1.87)	<0.001
Obesity (0=no, 1=yes)	1.26 (1.22:1.31)	<0.001	1.43 (1.38:1.49)	<0.001
Current smoker (0=no, 1=yes)	1.34 (1.26:1.43)	<0.001	0.90 (0.86:0.94)	<0.001
Daily drinker (0=no, 1=yes)	0.92 (0.86:0.98)	0.006	0.78 (0.76:0.81)	<0.001
BP classification[a]				
Optimal BP	1 (Reference)		1 (Reference)	
Prehypertension with normal BP	0.95 (0.91:1.00)	0.03	1.01 (0.96:1.07)	0.60
Prehypertension with high-normal BP	1.02 (0.97:1.06)	0.54	1.11 (1.05:1.17)	<0.001
Hypertension	1.17 (1.12:1.23)	<0.001	1.32 (1.25:1.38)	<0.001

Abbreviations: BP, blood pressure; CKD, chronic kidney disease.
Obesity was defined as body mass index (BMI) ⩾25 kg/m^2. BP classification was defined as follows: optimal BP, systolic blood pressure (SBP) <120 mm Hg and diastolic blood pressure (DBP) <80 mm Hg; prehypertension with normal BP, SBP 120–129 mm Hg and/or 80–84 mm Hg; prehypertension with high-normal BP, SBP 130–139 mm Hg and/or DBP 85–89 mm Hg; hypertension, SBP ⩾140 mm Hg and/or DBP ⩾90 mm Hg. Statistical significance was defined as $P<0.05$.
[a]BP classification: Odds ratio was adjusted for age, obesity, current smoking, and daily drinking.

of proteinuria, there was a positive association between current smoking and proteinuria in both genders (odds ratio (95% CI): 1.47 (1.38–1.56) in men and odds ratio (95% CI): 1.89 (1.15–3.11) in women; both $P<0.001$).

Effect of obesity on the association between CKD and BP classification

Among subjects without hypertension ($n=181,215$), the risk of CKD conferred by prehypertension with high-normal BP increased when these conditions were accompanied by obesity (⩾25 kg/m^2) in men (Figure 2a), but not in women (Figure 2b). Accordingly, we examined whether or not there was an interaction between obesity and prehypertension with high-normal BP on CKD risk among subjects without hypertension. Using a multivariable logistic regression analysis, we showed that there was an additive effect, but not a synergistic one, of obesity and prehypertension with high-normal BP on CKD risk in men (data not shown). Furthermore, we also examined whether there was an interaction between obesity and hypertension (⩾140/90 mm Hg) on CKD risk among all subjects ($n=232,025$). The results showed that there was no synergistic interaction in either gender (data not shown).

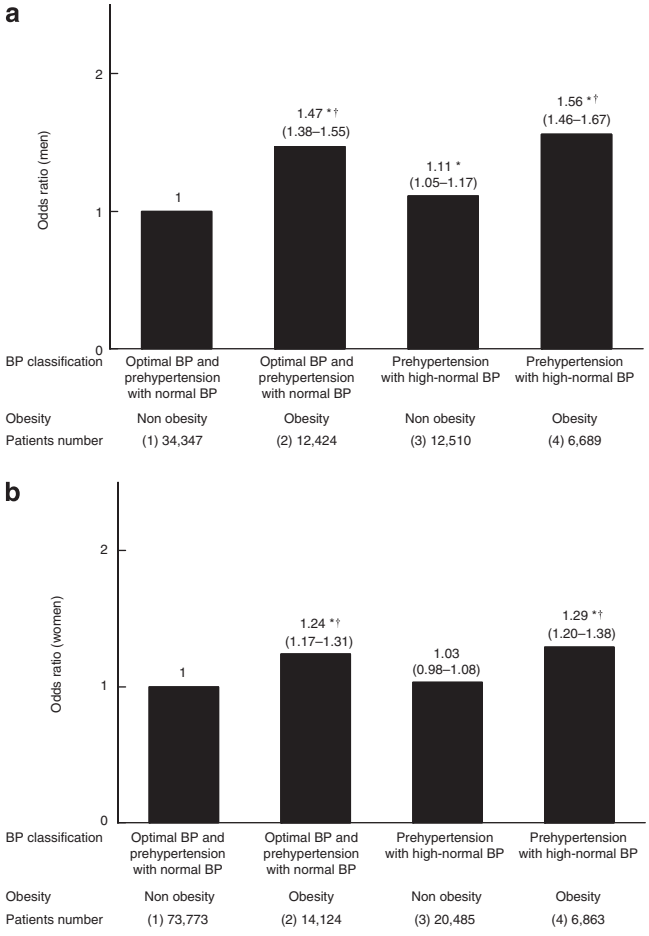

Figure 2 | Logistic regression analysis of chronic kidney disease risk among subjects without hypertension. The odds ratio (95% confidence interval) of chronic kidney disease risk in subjects with or without obesity and/or prehypertension with high-normal blood pressure (BP) is shown in men (**a**) and women (**b**). The analysis was adjusted for age, current smoking, and daily drinking. Chronic kidney disease was defined as estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2 and/or the presence of proteinuria (⩾1+). *$P<0.001$ versus group (1) and †$P<0.001$ versus group (3).

DISCUSSION

Prehypertension and CKD

In this nationwide study of 232,025 Japanese aged 20 years or older, we have demonstrated the prevalence of CKD across the diagnostic spectrum of BP classification. In the present study, the prevalence of CKD was 17.0% in men and 12.2% in women. The prevalence was lower than a previous Japanese report,[5] because the present study excluded treated hypertensive patients. In particular, we focused on the prevalence of CKD among subjects with prehypertension (16.7% in men and 12.2% in women). The prevalence of CKD among subjects with prehypertension with high-normal BP was greater in men than in women (18.1% versus 12.9%), and prehypertension with high-normal BP was an

independent risk factor for CKD in men, but not in women, even after adjustment for confounders.

Evidence is accumulating that prehypertension, and particularly a high-normal BP range, is associated with a variety of cardiovascular diseases and cardiovascular-associated and all-cause mortality;[15–17] however, information about the association of prehypertension with CKD is scarce in Japan.[18] Much as in other previous reports worldwide,[14–16] older age, higher prevalence of men, and obesity or obesity-related metabolic abnormalities were more prevalent in subjects with prehypertension than those with optimal BP (Table 2). These characteristics could partly explain the cardiovascular risk of prehypertesion;[15–17] however, our data show that the association between CKD and prehypertension with high-normal BP in men is independent of these confounders.

The increased risk of CKD among prehypertensive subjects with high-normal BP was recognized only in men; this means that the parallel increase of CKD in accordance with the level of severity of BP begins at an earlier phase in men than in women. This gender difference cannot be fully explained by the gender differences in metabolic factors or BP itself. It is speculated that it may be related to gender-specific differences in glomerular structure, hemodynamic condition, activity of local cytokines and hormones, gene expression, and/or the effects of sex hormones on kidney cells.[9,19]

As shown in several previous reports,[10–12] hypertension ($\geqslant$140/90 mm Hg) is a clear risk factor for CKD in both the genders. In the present study, we excluded 84,854 subjects who had been treated with anti-hypertensive medication, and included 50,810 subjects who had never been treated with anti-hypertensive medication. This exclusion rate suggests that about a quarter of hypertensive subjects have not been treated for their condition. This proportion is substantially improved as compared with a previous report,[20] but more health promotion to increase awareness and treatment of hypertension is still considered necessary.

Obesity, BP, and CKD

Obesity is an independent risk factor for CKD both in men and women (Table 3). Intriguingly, our data indicate that the risk of CKD conferred by prehypertension with high-normal BP in men increased when these conditions were accompanied by obesity (Figure 2a). There was an additive effect of obesity and prehypertension with high-normal BP on CKD risk in men.

Obesity-associated glucose and lipid abnormalities could partly explain the increased risk of CKD in obesity.[21,22] However, our data show that the increased risk of CKD conferred by obesity was independent of these confounders, although there was some lack of data on glucose and lipid parameters. There remain several other possible explanations for the risk of obesity. First, unmeasured obesity-associated factors, such as insulin resistance, inflammatory and oxidative stress, and abnormal adipocytokine production, may be involved in the increased risk of CKD in obesity.[22,23] Second, obesity has a fairly consistent effect on renal hemodynamics, suggestive of glomerular hypertension.[24,25] At an early phase, obesity is associated with an elevated GFR with a less pronounced increase, or even a decrease, in effective renal plasma flow, resulting in an increased filtration rate. This alteration, that is, a predominant decrease in afferent rather than efferent glomerular tone in obese subjects, may confer enhanced renal susceptibility toward damage when BP increase is superimposed.[24,25] Obesity-induced hyperfiltration, if continued for a certain period, can cause a decline in GFR, which may be one of the reasons why our data showed that obese subjects had a lower eGFR than nonobese subjects in both genders.

Lifestyle factors and CKD

Lifestyle factors, such as smoking and drinking, are also important contributors to CKD.[26] In the present study, an inverse association between CKD and current smoking was found (Table 3), despite the fact that several previous studies have identified smoking as an important risk factor in the promotion and progression of renal dysfunction in healthy subjects or those with complications.[27,28] Our study is a cross-sectional study, and thus there may have been artifacts due to the observation of sick subjects after they have changed their lifestyles. However, the effects of smoking on eGFR are still controversial.[27,29,30] In fact, we observed that male current smokers had a higher eGFR than male non-smokers, whereas no such association was found in women. On the other hand, our present results agree with previous reports;[27,29] in that we found a positive association between smoking and proteinuria in both genders, suggesting the possibility that smoking causes endothelial dysfunction, partly through an inflammatory or oxidative pathway.[28,29] It was also unexpected that there was an inverse association between the BP increase and the prevalence of current smoking (Table 2); this may have been attributable to one of the following: (1) Some of the smokers in the hypertensive group may have had knowledge that they were hypertensive, and may have ceased to smoke on the advice of their physicians. (2) There may have been a so-called survival effect, as smokers who develop hypertension were more likely to have died and thus not to have been included in the cross-sectional study. (3) Daytime BP under daily activity would likely be more elevated in smokers compared with non-smokers, even when there is no difference in the clinical or office BP between them (i.e., masked hypertension is more prevalent in smokers).[31]

Evidence on the association between CKD and alcohol intake has been scarce. We found that subjects with a daily drinking habit had a lower likelihood of CKD compared with those who had no alcohol intake. We could not assess the kinds or total amount of alcohol; therefore, to discuss this issue is beyond the scope of the present research. Further investigation with prospective or lifestyle interventional studies, such as smoking cessation studies, are warranted to better elucidate the impact of smoking or drinking on renal outcomes.

Several limitations of our study should be mentioned. First, we cannot infer a cause–effect relationship based on our cross-sectional data. Second, only a single measurement of serum creatinine, as well as only a single assessment of proteinuria, is not fully accurate, and thus there may be an underestimation of the true association between CKD and BP level. Third, subjects who participated in the present survey were generally healthy individuals who were interested in their health; therefore, the prevalence of prehypertension/hypertension or CKD may have been underestimated. Finally, little is known about the cost-effectiveness of screening male subjects with prehypertension and high-normal BP range for CKD; therefore, an additional study is needed to identify the most appropriate populations to undergo CKD screening.

CONCLUSION

Using a nationwide Japanese database, we show an increased prevalence of CKD across the diagnostic spectrum of hypertension. Among men, even in the state of prehypertension, high-normal BP, particularly when in conjunction with obesity, was an independent risk factor for CKD. Considering the fact that the prevalence of CKD and the incidence of end-stage renal disease are increasing in Japanese men,[5,8,9] these data have important clinical implications; as CKD is often asymptomatic but progressive, more attention must be paid to men and women with hypertension or obesity and to men even with high-normal BP for the early detection and prevention of CKD, or to delay the progression to renal failure.

MATERIALS AND METHODS

Study population

The methods of the study are detailed in the Supplementary Information section online. Briefly, based on a recent survey that showed that obesity and metabolic syndrome are not uncommon in Japan (http://www-bm.mhlw.go.jp/houdou/2008/04/h0430-2.html), the Japanese government started a new health-care strategy that targeted early diagnosis and intervention for metabolic syndrome from 2008 (Specific Health Checkups and Guidance System (Tokutei-Kensin)). In this new health-care system, people diagnosed with metabolic syndrome are obligated to receive repeated lifestyle guidance over a 6-month period after an annual health examination.

Thirteen of the prefectures participating in this nationwide project (Yamagata, Miyagi, Fukushima, Niigata, Tokyo, Kanagawa, Ibaraki, Osaka, Okayama, Kochi, Fukuoka, Miyazaki, and Okinawa) agreed on our study purpose and were included in the present analysis. The population surveyed included a total of 346,942 subjects (41% ($n = 141{,}938$) were men) above 20 years of age, for whom all the data necessary for our research purposes were available—namely, information about age, gender, BP, body mass index, habitual smoking or drinking, use of anti-hypertensive drugs, previous history of cardiovascular diseases (i.e., cardiac disease and stroke), and data about the serum creatinine level and dipstick urine test for proteinuria. This study was granted ethics approval from the respective institutional review boards. Data were sent to an independent data center called the NPO Japan Clinical Research Support Unit, and verified by trained staff.

Baseline measurement

At the baseline examination, all subjects completed a self-administered questionnaire about lifestyle factors (current smoking status, daily drinking), and provided medical information on treatment with anti-hypertensive drugs and a previous history of cardiac disease or stroke. The study physicians performed a physical examination of each subject and rechecked their medical history to improve the precision of the information.

According to the recommendations of the Ministry of Health, Labor and Welfare (http://www.mhlw.go.jp/bunya/shakaihosho/iryouseido01/info03a.html), BP was measured by trained observers using a standard sphygmomanometer or an automated device on the right arm after resting for 5 min in a seated position with the legs not crossed. Conversation and alcohol/caffeine consumption should also be avoided before measurement. Subjects were classified according to their BP level as follows: optimal BP (systolic BP/diastolic BP $< 120/80$ mm Hg), prehypertension[32] that comprises normal BP (systolic BP 120–129 mm Hg, diastolic BP 80–84 mm Hg or both) and high-normal BP (systolic BP 130–139 mm Hg, diastolic BP 85–89 mm Hg or both), and treated or untreated hypertension (systolic BP/diastolic BP $\geqslant 140/90$ mm Hg or usage of anti-hypertensive medication).[33]

Body height and weight were measured in light clothing without shoes, and the body mass index was calculated (kg/m^2). According to the Japan Society for the Study of Obesity,[34] obesity was defined as a body mass index $\geqslant 25$ kg/m^2.

Blood samples were collected after an overnight fast and were assayed within 24 h. For the purpose of our study, there were no missing data on the serum creatinine level, but there was a substantial lack of data on the glucose and lipid parameters (Supplementary Table S1 online). Freshly voided urine samples were tested by the dipstick methods in all subjects. Proteinuria was defined as $1+$ or more.

Definition of CKD

Serum creatinine was assayed by an enzymatic method. eGFR was derived using the following equation:

$$\text{eGFR (ml/min per 1.73 m}^2) = 194 \times \text{age (years)}^{-0.287} \times \text{serum creatinine (mg/dl)}^{-1.094} \text{ (if women } \times 0.739).[35]$$

Details about this equation are also shown in the Supplementary Information section. CKD was defined as either the presence of proteinuria or eGFR < 60 ml/min per 1.73 m^2. The clinical stages of CKD were classified according to the recommendations of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines[36]: Stage 1 or 2 (eGFR $\geqslant 60$ ml/min per 1.73 m^2 and the presence of proteinuria), Stage 3 (eGFR 30–59 ml/min per 1.73 m^2), Stage 4 (eGFR 15–29 ml/min per 1.73 m^2), and Stage 5 (eGFR $<$ 15 ml/min per 1.73 m^2).

Statistical analysis

All statistical analyses were performed with the SPSS version 18.0J software (SPSS, Chicago, IL). The differences of patient characteristics and BP values according to the BP classification were assessed using analysis of variance, and categorical parameters were compared with the χ^2-test. As there is a significant gender difference in the prevalence of CKD, we examined the association between CKD and the severity of BP classification separately in men and women. The odds ratio and 95% CI of each BP classification group (optimal BP group (reference) versus prehypertension with normal BP, prehypertension with high-normal BP, and untreated hypertension group) were calculated for the presence of CKD by multiple

logistic regression analysis. Finally, we used a multivariable logistic regression analysis to examine the effect of obesity on the association between CKD and BP classification, as well as whether or not there was an interaction between obesity and prehypertension with high-normal BP on CKD risk. Statistical significance was defined as $P<0.05$.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Table S1. Glucose and lipid parameters according the BP classification by gender.

Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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